

REMARKS/ARGUMENTS

In response to the Office Action of July 10, 2006, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claims 1, 13 and 15 have been amended. Claims 2-6, 12, 26 and 27 have been cancelled. Claims 32-122 are withdrawn from consideration. It is understood that claims 32-122, drawn to the non-elected inventions (Groups II-IV), will remain pending, albeit withdrawn from consideration on the merits at this time. Applicants retain the right to present the non-elected claims, 32-122, in a divisional application(s). Claims 1, 7-11, 13-25 and 28-122 remain pending in the instant application.

No new matter has been added by the amendments to the claims made herein.

Claim 1 has been amended to incorporate the subject matter of original claims 2, 3, 6, 12, 26 and 27. Claims 13 and 15 have been amended only to update claim dependency in accordance with the amendments made herein.

* Please note that the Examiner's comments applied in the Office Action are single spaced herein to clearly delineate the Examiner's comments from Applicants' comments.

Rejections under 35 USC 102

Claims 1, 7, 10-13, 15, 24, 28 and 30, as presented on May 1, 2006, stand rejected as allegedly being anticipated by US Patent 4,350,791 (Straub et al.).

The Examiner asserts that Straub discloses a process for producing a block copolymer comprising: (A) a vinylpyrrolidone polymer having terminal hydroxyl groups, and (B) a block copolymer formed by polymerization of ethyl 2,6-diisocyanatocaproate. The starting compound is polyvinylpyrrolidone which is formed by polymerization of N-vinyl-2-pyrrolidone in the presence of hydrogen peroxide-radical initiator in aqueous solution, col.2 lines 20-23; however, the organic solvent such as a lower alcohol, dioxane or tetrahydrofuran, or an aromatic solvent can be used, that is readable in the present claims 7, 13 and 15. A lower alcohol such as methanol, ethanol, isopropanol is advantageous to use, col. 2, lines 40-42. The step of producing a hydroxyl-terminated vinylpyrrolidone polymer in an alcoholic solvent is readable in step (a) in the present claim 1. Depending on the degree of polymerization of vinylpyrrolidone polymer and the molecular weight of the hydroxyl-containing monomer the functional polymerizable monomer such as allyl alcohol or hydroxypropylmethacrylamide can be added, col 2. Lines 63-68 and col.7, lines 1-3. The allyl alcohol and hydroxypropylmethacrylamide are within the scope of a chain transfer agent to control the molecular weight of N-vinylpyrrolidone polymer, and said chain transfer agent is responsive for producing a PVP-OH polymer. The obtained vinylpyrrolidone polymer is purified, col. 3, line 30. The step of producing a purified polyvinylpyrrolidone readable in the present claim 12. In the second step the obtained vinylpyrrolidone polymer is reacted with alpha, omega-diisocynato-alkanecarboxylic acid esters, for example, ethyl 2,6-diisocyanatocaproate, col. 3, line 32, in the presence of a conventional catalyst, col. 3, line 64. A catalyst in the present claim 1 can include any catalyst for polymerizing any monomer. The polymerizable monomer for producing a B-block polymer in the Straub invention is readable in the present claim 1. Example of suitable catalyst such as organic tin compound is readable in the present claim 10. The average molecular weight of the polyvinylpyrrolidone polymer is preferably within the range from 1,000 to 10,000, col. 3, lines 25-28. The Mw of at least 1,000 is readable in the present claim 24. Straub discloses a diblock copolymer and triblock copolymer based on N-vinylpyrrolidone polymer that is readable in present claims 28 and 30. The Examiner concludes that the invention as claimed in the

present claims 1, 7, 10-13, 15, 24, 28 and 30 is fully anticipated by the disclosure in the Straub invention.

Applicants respectfully disagree with the Examiner's assertions.

It has been established that in order for a claim to be anticipated each and every element as set forth in the claim must be found, either expressly or inherently described in a single prior art reference (see MPEP 2131).

Applicants respectfully submit that the process and block copolymers disclosed by Straub et al. are distinct from the process and block copolymers of the claimed invention.

The block copolymers of the described invention exhibit self-assembly into polymeric micelles and stabilized nanoparticles in aqueous solution (see the instant specification as originally filed at page 38, line 5 to page 41, line 1 and Figure 9). The instant Applicants have found that the hydroxyl-terminated poly (N-vinylpyrrolidone) which is used to form these block copolymers must be prepared by polymerizing N-vinyl-2-pyrrolidone in the presence of a radical initiator, a chain transfer agent and an alcoholic solvent in order for the block copolymers to exhibit the property of self-assembly into micelles (see the instant specification as originally filed at page 1, lines 5-22). Furthermore, once the hydroxyl-terminated poly (N-vinylpyrrolidone) is obtained, it is purified by dissolution followed by precipitation (see the instant

specification as originally filed at page 17, lines 2-16). The block copolymers produced by the described process can be prepared on an industrial scale and utilized in drug carrier systems (see the instant specification as originally filed at page 8, lines 7-9).

The block copolymers disclosed by Straub et al. are prepared from polymerization of vinylpyrrolidone and α,ω -Diisocyanato-alkanecarboxylic acid esters (see, for example, the abstract). According to the process of Straub et al. vinylpyrrolidone with hydroxyl end groups is obtained by free radical polymerization of N-vinylpyrrolid-2-one in the presence of hydrogen peroxide (as the free radical initiator) and a complex hydride (column 2, lines 11-19). In contrast to the process of the instant invention, Straub uses an alcoholic solvent only when using complex hydrides other than sodium boranate or lithium boronate (column 2, lines 19-50). The highly reactive group of complex hydrides whose use is suggested in column 2 are not chain transfer agents, but rather, strong bases that are not equivalent to the chain transfer agents used in the instant invention, such as 2-mercaptoethanol. Furthermore, Straub discloses only the use of isocyanates (column 1, lines 54-65) which are not used in the process of the instant invention. The block copolymers of Straub are prepared for utilization as plasma substitutes and as such must be of the

appropriate molecular weight to simulate the colloid-osmotic pressure of blood plasma (column 1, lines 18-23). Thus, micelles or nanoparticles could not be obtained with the block copolymers of Straub.

Accordingly, as evidenced by the above discussion, each and every element of the rejected claims can not be found described in the reference of Straub et al. Applicants respectfully submit that they have now pointed out how the process and block copolymers as instantly claimed distinguish over the process and block copolymers taught by Straub et al. and respectfully request that this rejection under 35 USC 102(b) now be withdrawn.

Claims 1, 9, 11, 12 and 28, as presented on May 1, 2006, stand rejected under 35 USC 102(e) as allegedly being anticipated by US 6,756,449 (Benz et al.).

The Examiner asserts that Benz discloses a block copolymer, wherein an A-block is a PVP-OH terminated polymer produced by radical polymerization (see col.9, lines 39-40) in the presence of a hydroxyl-terminated chain transfer agent, such as isopropoxyethanol, col.9, lines 30-42 and claim 65 at column 32. A radical initiator includes azo-bisisobutyronitrile (AIBN) initiator, col.11, lines 63-64, for the present claims 1 and 9. Claimed alcoholic solvent medium is readable for being an isopropoxyethanol. The PVP-OH polymer was precipitated, col. 12, line 16, and purified, for the present claim 12. A B-block polymer can be produced from a variety of polymerizable monomers, col. 6, lines 57-67; col. 7, lines 33-37; and col. 8, lines 1-67. The B-block copolymer can be produced using standard techniques, col. 9, lines 46-51. A catalyst in the present claim 1 for (b) step is inherent to any catalyst using standard techniques in Benz invention. The Examiner concludes that the claimed invention in the present claims 1, 9, 11, 12 and 28 is fully anticipated by the disclosure in the Benz invention.

Applicants respectfully disagree with the Examiner's assertions.

It has been established that in order for a claim to be anticipated each and every element as set forth in the claim must be found, either expressly or inherently described in a single prior art reference (see MPEP 2131).

Applicants respectfully submit that the process and block copolymers disclosed by Benz et al. are distinct from the process and block copolymers of the claimed invention.

The block copolymers of the described invention exhibit self-assembly into polymeric micelles and stabilized nanoparticles in aqueous solution (see the instant specification as originally filed at page 38, line 5 to page 41, line 1 and Figure 9). The instant Applicants have found that the hydroxyl-terminated poly (N-vinylpyrrolidone) which is used to form these block copolymers must be prepared by polymerizing N-vinyl-2-pyrrolidone in the presence of a radical initiator, a chain transfer agent and an alcoholic solvent in order for the block copolymers to exhibit the property of self-assembly into micelles (see the instant specification as originally filed at page 1, lines 5-22). Furthermore, once the hydroxyl-terminated poly (N-vinylpyrrolidone) is obtained, it is purified by dissolution followed by precipitation (see the instant specification as originally filed at page 17, lines 2-16). The

hydroxyl-terminated poly (N-vinylpyrrolidone) is then polymerized with monomers or comonomers such as 3,6-dimethyl-1,4-dioxane-2,5-dione, ϵ -caprolactone, γ -caprolactone poly(D,L-lactide), poly(D-lactide), poly (L-lactide), poly(ϵ -caprolactone) and poly (γ -caprolactone) (see the instant specification as originally filed at page 1, lines 13-18 and page 18, lines 12-21). The block copolymers produced by the described process can be prepared on an industrial scale and utilized in drug carrier systems (see the instant specification as originally filed at page 8, lines 7-9).

The block polymers disclosed by Benz et al. are designated A_nB block copolymers; including A blocks of poly(vinyl pyrrolidone) units and B blocks of urethane groups, urea groups, imide groups, amide groups, ether groups, ester groups and combinations thereof (see abstract). Benz does not teach the polymerization of poly(vinyl pyrrolidone) with any of the monomers or comonomers that are taught in the instant invention (step (b) of claim 1 as amended herein). In the preparation of their poly(vinyl pyrrolidone) Benz et al. use isopropoxyethanol as a chain transfer agent and use AIBN as a radical initiator (column 9, lines 20-45 and Example 1). However, in contrast to the process of the instant invention, Benz et al. do not use an alcoholic solvent. Furthermore, the block polymers of Benz are used to provide surface coatings and medical devices such as tubing (column 1, lines 27-30 and Examples 36, 37

and 38). As surface coatings, these block polymers are prepared to exhibit a lubricious (slippery) property (column 5, lines 15-24). Thus, micelles or nanoparticles could not be obtained with the block copolymers of Benz.

Accordingly, as evidenced by the above discussion, each and every element of the rejected claims can not be found described in the reference of Benz et al. Applicants respectfully submit that they have now pointed out how the process and block copolymers as instantly claimed distinguish over the process and block copolymers taught by Benz et al. and respectfully request that this rejection under 35 USC 102(e) now be withdrawn.

Rejections under 35 USC 103(a)

Claim 8, as presented on May 1, 2006, stands rejected under 35 USC 103(a) as allegedly being unpatentable over US 4,350,791 (Straub et al.) further in view of US 4,699,950 (Sato et al).

The Examiner asserts that Straub does not disclose a chain transfer agent that is a thiol derivative as in the present claim 8. Sato discloses a chain transfer agent having a thiol end group.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art to modify a process for producing a PVP-OH in Straub invention by employing a thiol chain transfer agent as disclosed in the Sato invention, since any chain transfer agent works within the same expectation to control a molecular weight of the resulting PVP-OH polymer in the present claim 1.

Applicants respectfully disagree with the Examiner's assertions.

It was established above in the section covering the rejection

under 102(b), that the process and block copolymers disclosed by Straub et al. are distinct from the process and block copolymers of the claimed invention. Thus, even if one of ordinary skill in the art were to use a thiol derivative as disclosed by Sato as a chain transfer agent in the process of Straub, one would still not arrive at the instant invention since the use of a thiol derivative would not produce block copolymers that can form micelles and nanoparticles.

Accordingly, it is respectfully submitted that the combination of Straub et al. and Sato et al. fails to reasonably teach or suggest to one of ordinary skill in the biochemical arts the elements of Applicants' process as specifically set forth in claims 1 and 8 as presented herein. Applicants respectfully submit that the claimed process and block polymers distinguish over the prior art and request that this rejection of claim 8 under 35 USC 103(a) now be withdrawn.

Claims 2-6, 9, 14, 16-23, 25-27, 29 and 31, as presented on May 1, 2006, stand rejected under 35 USC 103(a) as allegedly being unpatentable over US 4,350,791 (Straub et al.) further in view of US 6,338,859 or Article "Graft Copolymer for Biomedical Applications Prepared by Free Radical Polymerization of (poly(L-lactide) Macromonomers with Vinyl and Acrylic Monomers" by Jose Luis Equiburu et al., November 1995, cited by Applicants; or Article "Novel Amphiphilic Diblock Copolymer of Low Molecular Weight Poly (N-vinylpyrrolidone)-block-poly (D,L-lactide): Synthesis, Characterization and Micellization" by Laibin Luo et al., December 2003, cited by Applicants; or Article "Novel Polymeric Micelles Based on the Amphiphilic Diblock Copolymer (N-

vinylpyrrolidone)-block-poly (D,L-lactide)" by Amina Benahmed et al., September 200, cited by Applicants.

The Examiner asserts that the primary reference Straub does not disclose the claimed cyclic (co)monomer for producing a block polymer that is a degradable polyester. Each of the secondary references discloses a diblock copolymer having a degradable polyester based on poly(L-lactide) macromonomers and a hydrophilic PVP-OH block polymer. The Examiner concludes that it would have been obvious to one of ordinary skill in the art to substitute a block polymer formed by polymerization of ethyl 2,6-diisocyanatocaproate in Straub with a degradable polyester based on poly(L-lactide) macromonomer as taught in each secondary reference for the purposes of obtaining the claimed requirement and since any polymerizable monomers for producing a hydrophobic block are readable in the present claim 1. The B-block polymer in each cited reference works within the same expectation for producing an amphiphilic block copolymer. There is no showing of unexpected results derived from said replacement.

Applicants respectfully disagree with the Examiner's assertions.

It was established above in the section covering the rejection under 102(b), that the process and block copolymers disclosed by Straub et al. are distinct from the process and block copolymers of the claimed invention.

The filing date of the instant application is December 2, 2003. The Luo et al. reference was received by the "Macromolecules" journal on December 15, 2003 and published on the web on May 4, 2004. Thus, the Luo et al. reference can not be considered prior art.

The requirements for use of crown ether and dialysis and centrifugation for the copolymer purification disclosed in the Leroux et al. and Benahmed et al. references are not desirable on

an industrial scale (see the instant specification as originally filed at page 6, line 15 to page 7, line 14).

Thus, even if one of ordinary skill in the art were to use a polyester monomer as disclosed by Leroux and/or Benahmed in the process of Straub, one would still not arrive at the instant invention since the process is not amenable on an industrial scale.

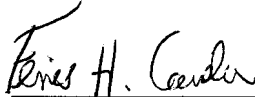
No alcoholic solvents are used in the process disclosed by Equiburu et al. Furthermore, micelles or nanoparticles could not be obtained with the block copolymers of Equiburu. Thus, even if one of ordinary skill in the art were to use a polyester monomer as disclosed by Equiburu in the process of Straub, one would still not arrive at the instant invention since the use of a polyester monomer would not produce block copolymers that can form micelles and nanoparticles.

Accordingly, it is respectfully submitted that the combination of Straub et al.; Luo et al.; Leroux et al.; Equiburu et al. and Benahmed et al. fails to reasonably teach or suggest to one of ordinary skill in the biochemical arts the elements of Applicants' process and block polymers as specifically set forth in the claims as presented herein. Applicants respectfully submit that the claimed process and block polymers distinguish over the prior art and request that this rejection of claims 2-6, 9, 14, 16-23, 25-27, 29 and 31 under 35 USC 103(a) now be withdrawn.

CONCLUSION

In light of the foregoing remarks and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of this application is courteously requested.

Respectfully submitted,



Ferris H. Lander
Registration # 43,377

McHale & Slavin, P.A.
2855 PGA Boulevard
Palm Beach Gardens, FL 33410
(561) 625-6575 (Voice)
(561) 625-6572 (Fax)

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